What Computational Chemistry Can Do for You

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1. Introduction

Quantum chemistry is capable of calculating a wide range of electronic and thermodynamic properties of interest to a chemist or physicist. Calculations can be used both to predict the results of future experiments and to aid in the interpretation of existing results. Quantum chemistry can also be applied to biological processes such as toxicity and carcinogenicity. Here we will present three examples of how quantum chemistry can be used to investigate the biological activity of a class of environmentally significant organic compounds, polycyclic aromatic hydrocarbons (PAHs).

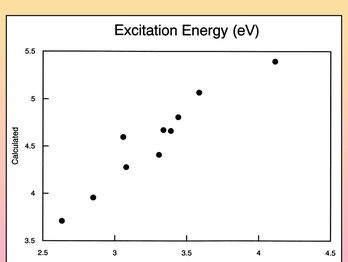
3. Conclusion

Quantum chemistry calculations can be a fast and inexpensive alternative to the experiments necessary to determine the biological activity of many types of compounds. Although calculations will never eliminate the need for experiment, they can be a valuable tool for the prediction of and understanding of experimental results and provide insight into biological mechanisms that may be unavailable to the experimentalist.

2. Applications

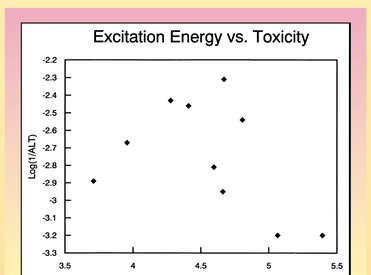
Photo-Induced toxicity

Polycyclic aromatic hydrocarbons are not generally toxic in conventional laboratory tests. However many become extremely toxic when exposed to sunlight. The relationship between chemical structure and photo-induced toxicity depends on many complex processes including molecular stability and light absorbance. Previous authors have sought a relationship between a molecules photo-induced toxicity and its Highest Occupied Molecular Orbital energy - Lowest Unoccupied Molecular Orbital energy (HOMO-LUMO) gap. While some correlation is seen, the HOMO-LUMO gap does not correspond to any physical property and provides no insight to the mechanism of photo-induced toxicity. We have therefore attempted to explore the phenomenon of photo-induced toxicity using the single-excitation CI (CIS) method. This method models the process of electronic photo-excitation that would result from exposure to sunlight or in a UV/visible spectrometer in the laboratory. The CIS method also has the advantage of providing insight into the mechanism of photo-induced toxicity, i.e., the particular orbitals involved in the electronic transition, oscillator strengths, etc.



The lowest singlet excitation energy was calculated using the RCIS/6-311G(p,d) method. Good agreement is seen between the calculated excitation energies and experimental fluorescence data[1].

[1] Morgan, D., Warshawsky, D., Atkinson, T.; Photochemistry and Photobiology, Vol 25, pp 31-38, 1977.

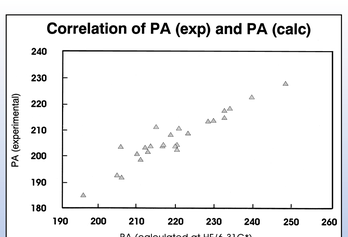


PAHs exhibiting the highest amount of photo-induced toxicity are seen to fall within an excitation energy window of 3.7 to 4.8 eV.

Correlation between photo-induced toxicity and singlet excitation energies calculated using the CIS method has been demonstrated. The CIS method can thus be used to predict the amount of photo-induced toxicity to be expected in compounds with unknown toxicity. Careful study of the CIS results may also yield further insight into the relationship between structure and photo-induced toxicity.

Carcinogenicity

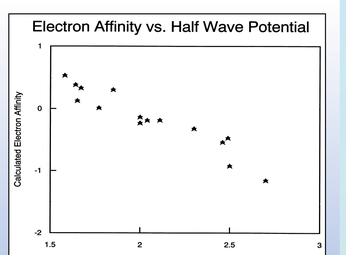
Polycyclic aromatic hydrocarbons have been implicated as composing one of the largest classes of environmental carcinogens. One determinative method for the detection of PAHs that minimizes interferences due to aliphatic hydrocarbons is negative ion chemical ionization mass spectrometry. Often the more carcinogenic PAHs are enhanced compared with the less carcinogenic, e.g., benzo[a]pyrene and benzo[e]pyrene. The enhanced negative ion sensitivities are often compared with either the corresponding positive ion chemical ionization mode or traditional electron impact ionization. The ratios of negative ion to positive ion sensitivities for many PAHs have been determined under chemical ionization conditions. This led to ratios differing by three orders of magnitude. Calculation of ion sensitivities could therefore be a useful tool in the prediction of the level of carcinogenicity a compound will exhibit.

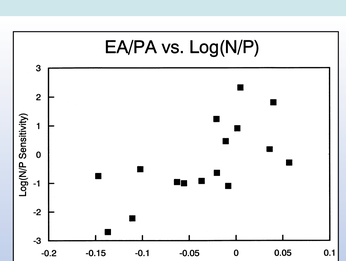


Left figure: Proton affinities for several PAHs were calculated at the HF/6-31G(d) level of theory.

Right figure: Electron affinities for several PAHs were calculated at the HF/6-311G(p,d) level of theory. Good agreement is seen between calculated electron affinity and experimental polarographic half wave potentials[1].

[1] Bergman, J.; Transactions of the Faraday Society, Vol 50, pp 829, 1954.





The relationship between ion sensitivities and calculated quantities.

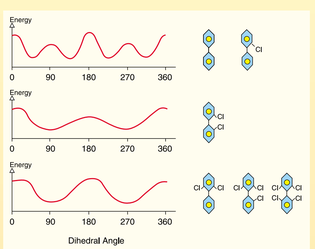
	Benzo[a]pyrene	Benzo[e]pyrene
	Very Carcinogenic	Not Carcinogenic
Log(N/P Sensitivity)	+2.60	-0.33
100 x Calculated EA/PA	+3.04	-2.41

As this table shows, for the two isomers benzo[a]pyrene and benzo[e]pyrene, the extreme difference in carcinogenicity is reflected in both the difference in the ratio of negative to positive ion sensitivity and in the calculated electron affinity to proton affinity ratio.

Calculation of electron affinity and proton affinity has been shown to provide a fair estimate of ion sensitivities. This can be used to estimate the level of carcinogenicity a compound will exhibit.

Dioxin-Type Toxicity of Polychlorobiphenyls

Many studies on the toxicity of tetrachlorodibenzo-p-dioxins have been undertaken. It is believed that an important factor in the toxicity of dioxins is their specific and high affinity binding to the receptor sites of certain proteins. Many classes of PAHs, such as polychlorinated biphenyls (PCBs), are also observed to exhibit dioxin-type toxicity. The number and location of chlorine atoms present on the biphenyl molecule has a dramatic effect on the observed toxicity of the PCB. It is likely that the chlorine atoms affect the ability of the biphenyl to assume a planar conformation necessary to mimic the shape of dioxin and exhibit dioxin-type toxicity. We have therefore performed calculations to qualitatively map the potential energy surface and quantitatively determine the barriers of rotation for several model PCBs.



The location of local minima and maxima was found to vary between different PCB compounds. The three possible qualitatively different potential energy surfaces as a function of dihedral angle are given at left.

Compound	Calculated Barrier To Rotation	Calculated Torsion Angle	Toxicity Relative to 2,3,7,8-TCDD[1]
B	6.6 kJ/Mol	45.5	
3,3',4,4'-TCB			0.0027
3,3',4,4',5,5'-HCB			0.0016
2-MCB	43.1 kJ/Mol	64.3	
2,3,3',4,4'-PCB			0.0011
2,3,4,4',5-PCB			0.000095
2,3,3',4,4',5-HCB			0.000135
2,2'-DCB	94.2 kJ/Mol	91.4	
2,2',3,3',4,4',5-HCB			0.000016
2,6-DCB	104.8 kJ/Mol	90.0	
2,3,3',4,4',6-HCB			<0.0000072
2,2',6-TCB	252.3 kJ/Mol	90.0	
2,2',3,3',4,4',6-HCB			<0.0000072
2,2',6,6'-HCB	514.4 kJ/Mol	90.0	
2,2',3,3',4,4',6,6'-OCB			<0.0000072

The calculation of barriers to rotation has been shown to be a good indication of the dioxin-type toxicity of PCBs. The calculated values are found to be somewhat larger than experimental values and further work is underway to more accurately model the rotation process. Nonetheless, calculation of barriers to rotation can provide a good estimation of dioxin-type toxicity of PCBs and similar chlorinated PAHs possessing internal rotation such as benzyltoluenes and diphenyl ethers.

Barriers to rotation were calculated at the HF/6-31G(p,d) level of theory. The magnitudes of the barriers to rotation are seen to be strongly dependant on the number of ortho chlorine atoms present. Good agreement between the barrier to rotation and toxicity is observed.

[1] Smith, L., Schwartz, T., Faltz, K.; Chemosphere, Vol 21, No 9, pp 1063-1085, 1990.